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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/250,056	02/12/1999	JAMES D. MARKS	2307E-852	1647

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EXAMINER	
HELMS, LARRY RONALD	
ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 12/31/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/250,056	MARKS ET AL.	
	Examiner	Art Unit	
	Larry R. Helms	1642	

-- The MAILING DATE of this communication appears n the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 September 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-15,34-44,53 and 54* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-13,34-42,53 and 54* is/are rejected.

7)☒ Claim(s) *14,15,43 and 44* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Claim 34 has been amended.

Claims 16-22 have been canceled.

2. Claims 1, 3-15, 34-44, 53-54 are pending and under examination.

3. The text of those sections of Title 35 U.S.C. code not included in this office action can be found in a prior Office Action.

Oath/Declaration

4. The Examiner acknowledges that a new oath is being executed, however, he oath or declaration is still defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is still defective because:

It does not state that the person making the oath or declaration has reviewed and understands the contents of the specification, including the claims, as amended by any amendment [emphasis added] specifically referred to in the oath or declaration.

Claim Objection

5. Claim 53 is objected to because it depends on a canceled claim, claim 16.

Rejections Withdrawn

6. The rejection of claims 34-44, 53-54 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of the amendments to the claims.

7. The rejection of claims 34-38 and 53-54, under 35 U.S.C. 112, first paragraph, is withdrawn in view of the amendments to the claims.

Response to Arguments

8. The rejection of claims 3-13, 39-42 under 35 U.S.C. 112, first paragraph, is maintained.

The response filed 9/17/03 has been carefully considered but has been deemed to be not persuasive. The response states that "**The Examiner, however, fails to address the substantive arguments provided in the previous response explaining why the pending claims are fully enabled**" and "**The examiner, however, has failed to provide any objective evidence whatsoever in support of this assertion** " (that the claimed antibodies would not bind c-erbB2) and If the antibody does not specifically

bind c-erbB2 and internalize then it is not within the literal scope of the claims and in the instant case "**inoperable embodiments are readily ascertained**" and the examiner admits that it is known how to make substitutions and calculate 70% and produce a protein that contains one or two CDRs (see pages 5-7 of response).

In response to these arguments, the examiner has addressed all arguments and will address them again herein. Claim 1 has not been included in this rejection because it is fully enabled, therefore although the rejected claims depend from claim 1 they are not enabled. While the examiner acknowledged one can make antibodies that are 70%, and have one or two CDRs, it is not clear how one skill in the art would determine how to use such antibodies or make such antibodies that are internalized and bind c-erbB2. Although the specification discloses making a large library of antibodies and assays for binding, it as acknowledged in the specification that "since antibodies which are internalized are likely to be rare" (see page 69, lines 25). Thus it appears that antibodies that are internalized are rare and as evidenced from the cited art(see below) that antibodies as claimed would be even more rare. The claims do encompass antibodies that are only 70% identical to SEQ ID NO:1 or 2 and have alterations in the CDRs and antibodies that only have one or two CDRs from SEQ ID NO:1 or 2. As discussed previously it is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target

epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc Natl Acad Sci USA 1982 Vol 79 page 1979). Rudikoff et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. Further, as evidenced by Adair et al. (PCT GB90/02017) transfer of CDR regions alone are often not sufficient to provide satisfactory binding activity in the CDR-grafted product (p. 4). Panka et al (Proc Natl Acad Sci USA Vol 85 3080-3084 5/88) demonstrate that a single amino acid substitution of serine for alanine results in decreased affinity. In at least one case it is well known that an amino acid residue in the framework region is involved in antigen binding (Amit et al Science Vol 233 747-753 1986). It is unlikely that antibodies as defined by the claims which may contain less than the full complement of CDRs from the heavy and light chain variable regions have the required binding function.

Claims 4 and 39 recite 70% sequence identity, however, sequence alignment between two sequences has no common meaning in the art. See George et al; "Current

Methods in Sequence Comparison and Analysis", in Macromolecular Sequencing and Synthesis, Selected Methods and Applications, pages 127-149 1988, Alan R. Liss, Inc and Barton et al "Protein Sequence Alignment and Database Scanning" in Protein Structure Prediction, A Practical Approach, 1996 IRL Press at Oxford University Press, Oxford, UK, pages 31-63). Barton et al teach that the "results of the analysis are entirely dependent on the choice of scoring results" (page 130, col 1-2, bridging paragraph). George et al teach that percent sequence identity is not an objective property of molecules but is a value arrived at by using algorithms (page 130, columns 1-2, bridging paragraph). One skilled in the art would reasonably conclude that methods of aligning amino acid sequences also depends on the choice of scoring results and the use of algorithms. The scoring of gaps when comparing one amino acid sequence to another introduces uncertainty as to the percent of similarity and the manner of alignment between two sequences.

The specification teaches a variety of algorithms for sequence (see pages 9-12) however the specification apparently lacks any particular guidance or specific method for determining 70% sequence identity. Therefore, it remains unclear what sort of alignment is allowed (i.e., gaps, mismatches) and which amino acid residues are considered to be similar.

Thus the prior art teaches that antibodies that do not have a full set of CDRs from the light and the heavy chain of a specific antibody do not bind antigen as evidenced from Rudikoff, Amit, and Panka. The prior art addresses antibodies as defined by the claims which would not bind antigen. The prior art teaches that it is unpredictable which

CDRs and frameworks (one or two in each chain as defined by the claims) to only substitute or which residues to maintain to obtain the required binding. The specification has not taught how to make antibodies as broadly defined by the claims that bind c-erbB2 and internalize.

The response then states that if it is the examiners position that the antibodies recited in the claims "**would not function**" as claimed then the examiner should make a utility rejection (see page 8 of response). In response to this argument, the rejection is based on the requirements under 112 first paragraph for how to make and use. The utility rejection does not apply because antibodies to cerbB2 have a substantial utility. The claims are rejected under 112 first because one skill in the art would not know how to make and use such broadly claimed antibodies.

Although the specification teaches assays for determining binding of an antibody, the rejection is maintained because just because one teaches an assay does not enable one to make and use antibodies because the specification does not disclose which residues of the myriad in the heavy and light chain to alter and still obtain an antibody that binds c-erbB2 and is internalized, which as evidenced from the specification is "rare" or unpredictable. Although screening antibodies is routine, it is not routine to determine which of the myriad of residues to alter or which one or two CDRs to use and which of the myriad of other CDRs to combine to the one or two CDRs or which antibodies that are only 70% and which residues to alter result in an antibodies that have the required c-erbB2 binding and internalize. Therefore, the rejection is maintained.

9. The rejection of claims 1, 34-38, 53-54 under 35 U.S.C. 103(a) as being unpatentable over Xu et al (int. J. Cancer 53:401-8, 1993) and further in view of Bird et al (Science 242:423-426, 1988, PTO-892 part of #15) and Chaudhary et al (PNAS 87:1066-70, 1990) is maintained.

The response filed 9/17/03 has been carefully considured but is deemed not to be persuasive. The response seems to put arguments together for the 103 rejections in the Office Action using Xu, Maier, and Shawver. The response states that the references do not teach a single chain antibody or an immunotoxin and the examiner relies on Bird and Chaudhary to teach single chains and immunotoxins. (see page 9 of response). The response states that the examiner relies on references teaching "**complete antibodies**" and relies on methods of making to construct an obvious rejection and "**the claims at issue define compounds (single-chain antibodies), not methods**" and the existence of a general method "**is essentially irrelevant to the question whether the specific molecules themselves would have been obvious**" and the existence of a full length antibody does not render obvious the existence of a single chain antibody and the examiner failed to establish that the full length antibodies even bind the recited epitopes (see page 10 of response).

In response to these arguments, while it is true that Xu, Maier, and Shawver teach internalizing antibodies, it would have been obvious to produce single chain antibodies. The examiner is well aware of the claims directed to products, however, it is

obvious to produce single chain antibodies as taught by Bird and Chaudhary. Bird specifically teach the advantages of such for a number of applications because of their small size such as being less immunogenic and having benefit for imaging of cancer (see page 426). Chaudhary teach the advantages of such immunotoxins for the ability to kill cells (see abstract). As such it would have been obvious to produce single chain antibodies of the antibodies of Xu, Maier, and Shawver for the advantages taught by Bird and Chaudhary.

The response states that "**there is no such burden where the ancillary references (Bird et al and Chaudhary et al) cited by the Examiner do not support a proper obviousness rejection under prevailing law**" (see page 10 of response)(this is in reference to the in re Best part of the rejection). In response to this argument, the rejection is proper and the burden was properly shifted to applicants and no such distinction was shown.

The response states the rejection is in hindsight (see page 11 of response) and the rejection is based on "obvious to try" (see page 11 of response). In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*,

443 F.2d 1392, 170 USPQ 209 (CCPA 1971). In addition the combined references make the claimed invention obvious as discussed above.

10. The rejection of claims 1, 34-38, 53-54 under 35 U.S.C. 103(a) as being unpatentable over Maier et al (Cancer Res 51:5361-5369, 1991) and further in view of Bird et al (Science 242:423-426, 1988, PTO-892 part of #15) and Chaudhary et al (PNAS 87:1066-70, 1990) is maintained.

The response filed 9/17/03 has been carefully considered but is deemed not to be persuasive. The response combines the arguments in one rejection and as such the response to these arguments have been addressed above.

11. The rejection of claims 1, 34-38, 53-54 under 35 U.S.C. 103(a) as being unpatentable over Shawver et al (Cancer Res 54:1367-1373, 1994) and further in view of Bird et al (Science 242:423-426, 1988, PTO-892 part of #15) and Chaudhary et al (PNAS 87:1066-70, 1990) is maintained.

The response filed 9/17/03 has been carefully considered but is deemed not to be persuasive. The response combines the arguments in one rejection and as such the response to these arguments have been addressed above.

12. Applicants request for an interview is acknowledged and will be granted upon request. Although applicant requested an interview prior to this Office Action; this Office Action has been set forth in view of administrative procedures and time constraints. The examiner apologizes for any inconveniences to applicant in this matter.

Summary

13. No claims are allowed. Claims 14-15, 43-44 are objected to.

14. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D, whose telephone number is (703) 306-5879. The examiner can normally be reached on Monday through Friday from 7:00 am to 4:30 pm, with alternate Fridays off. If attempts to reach the examiner by

telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

16. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 308-4242.

Respectfully,

Larry R. Helms Ph.D.